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Postoperative analgesic efficacy of ketamine added to bupivacaine in ultrasound guided transversus abdominis plane block for laparoscopic cholecystectomy

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Abstract

Aim: The aim of this study was to evaluate the efficacy of bupivacaine versus bupivacaine plus ketamine provided by Transversus Abdominis Plane (TAP) block for postoperative pain after elective laparoscopic cholecystectomy. Material and Method: A total of 120 patients were included in the study. The patients in Group B (n=60) received ultrasonography-guided bilateral subcostal TAP block with 20 ml of bupivacaine 1 mg kg-1 + 0.9% saline in each area, whereas the patients in Group BK (n=60) received bupivacaine 1 mg kg-1 with ketamine 0.5 mg kg-1 + 0.9% saline combination. Results: A total of 108 patients completed the study (Group B:53 and Group BK:55). In Group BK, postoperatively at 0, 2nd, 4th and 24th hours visual analog scale (VAS) scores at rest and 0, 2nd, 4th, 12th and 24th hours dynamic VAS scores were significantly lower than Group B ($p<0.05$). Moreover, in Group BK the time to first analgesic requirement was significantly later than in Group B ($p<0.0001$). We could not find any significant difference between the groups in terms of the total tramadol consumption. Discussion: We conclude that TAP block with bupivacaine plus ketamine rather than bupivacaine alone increases the time until the first request for rescue analgesia and lowers pain scores after laparoscopic cholecystectomy.

Keywords

Nerve Block; Ultrasonography; Bupivacaine; Ketamine; Analgesia

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Introduction

Laparoscopic cholecystectomy, one of the most common surgical endoscopic interventions today, is associated with the lesser intensity of incision-related pain than its 'open' variant counterpart [1]. Despite the minimally invasive nature, pain can be moderate to severe in the immediate postoperative period [2,3]. The goal of the treatment of postoperative pain is to eliminate or minimize the pain, accelerate recovery, and avoid potential side effects which may be associated with the treatment [2]. Numerous modalities have been employed to alleviate pain after laparoscopic cholecystectomy, which includes non-steroidal anti-inflammatory drugs, opioids, local anesthetic infiltration, thoracic epidural block and multimodal analgesia [4]. Transversus abdominis plane (TAP) block, a popular analgesic technique since its first description by Rafiin [5] in 2001 which may provide up to 24 hours of analgesia, may be an interesting analgesic option for the patients undergoing laparoscopic surgery. Ultrasonography-guided techniques may provide the advantage of being effective and safe through direct needle visualization; however, many recently published studies that use ultrasonography have reported conflicting analgesic results [6-8]. Through the wider use of peripheral block applications in recent years, the quality and duration of the block have become important and local anesthetics have been used in combination with adjuvant agents [9].

Therefore, we assessed to analyze the effect of bupivacaine versus bupivacaine plus ketamine in ultrasound-guided subcostal TAP block for laparoscopic cholecystectomy. Our primary outcomes were to assess the pain scores and tramadol consumption during postoperative 24 hours between the groups. Secondary outcomes were heart rate (HR) and blood pressure measurements throughout the operation, side effects in the preoperative period, and consumption of rescue analgesics during 24-hour follow-up.

Material and Method

Written informed consent was obtained from each patient. The study protocol was approved by the Local Ethics Committee and the Australian New Zealand Clinical Trials Registry (Ref: ACTRN12616001708448). The study was conducted in accordance with the principles of the Declaration of Helsinki. This was a single-center, prospective observational study. This study was conducted with ASA (American Society of Anesthesiologist) I-II patients aged between 18 and 75 years who were scheduled for elective laparoscopic cholecystectomy. The exclusion criteria included mental disorder, allergy to the respective drugs, a body mass index (BMI) greater than 30 kg m^{2-1} and language problem.

The patients were premedicated with intravenous (IV) midazolam (Zolamid®, Defarma, Ankara, Turkey) 0.01-0.02 mg kg^{-1}. Following the monitoring, the patients were intubated after the administration of fentanyl (Talinat®, Vem, Istanbul, Turkey) 1-2 mcg kg^{-1}, propofol (Propofol 2% Fresenius®, Fresenius Kabi, Bad Homburg von der Höhe, Germany) 2-3 mg kg^{-1} and rocuronium (Curon®, Mustafa Nevzat, Istanbul, Turkey) 0.6 mg kg^{-1}. For the maintenance of anesthesia, a minimum alveolar concentration of 1% for sevoflurane (Sevorane®Likit 100%, AbbVie, Queenborough Kent, England) in a 50% air + 50% O_2 mixture was administered at 1 L min^{-1} flow rate.

Following the intubation of the patient, the TAP block was applied under the guidance of ultrasonography (Esaote®, MyLab-30Gold Cardiovascular, Florence, Italy) before starting the surgery. The TAP block was performed by a single anesthesiologist experienced in TAP block. Prior to the application, the abdomen was cleansed with an antiseptic solution, and the 15-MHz linear transducer probe was covered using a sterile ultrasound probe cover. The probe was placed obliquely on the upper abdominal wall along the subcostal margin near the midline. The rectus abdominis muscle was identified first. Then the ultrasound probe was gradually moved laterally and obliquely along the subcostal margin, and the transversus abdominis muscle was identified lying posterior to the rectus muscle. The subcostal TAP block was bilaterally applied into the plane between the rectus abdominis and transversus abdominis muscles using a needle (80 mm 22 G, Stimuplex® Ultra, B. Braun Melsungen AG, Germany). The patients were divided into two groups depending on the agent used for the TAP block:

Group B (n=60): Patients who received subcostal TAP block with 20 ml bupivacaine (Bustesin®, Vem, Ankara, Turkey) 1 mg kg^{-1} + saline bilaterally.

Group BK (n=60): Patients who underwent subcostal TAP block with 20 ml bupivacaine 1 mg kg^{-1} + ketamine (Ketalar®, Pfizer, Istanbul, Turkey) 0.5 mg kg^{-1} + saline bilaterally.

After the TAP block was applied, the operation was started. During the operation, HR and mean arterial pressure (MAP) were recorded for each patient.

All patients received intravenous patient-controlled analgesia (PCA) (CADD-Legacy® PCA, Smiths Medical Inc, Minneapolis, MN, USA) for postoperative pain control. An IV solution of 90 ml saline + 10 ml tramadol (Tramosel® 50 mg ml^{-1}, Haver Pharma, Istanbul, Turkey) was prepared. The mode of PCA was a bolus of 5 ml, a lockout interval of 20 minutes, and no continuous infusion. To evaluate postoperative pain, a visual analog scale (VAS) (where 0=no pain, 10=worst imaginable pain) was applied at rest and a dynamic visual analog scale (DVAS) was used in case of coughing and a deep breath. Data regarding the need for rescue analgesic and the total tramadol consumption during 24h follow-up was recorded. Diclofenac sodium (Dikloron®, DEVA, Istanbul, Turkey) 75 mg was administered intramuscularly (IM) as rescue analgesic. Postoperative complications and patient satisfaction (very satisfied, satisfied, undecided, not satisfied) were evaluated.

Statistical Analysis

Version 3.1.9.2 of G power was used to determine the sample size. In the study, the expected effect size for the t-test was found to be d = 0.5 (theoretical) and alpha 0.05, power: 0.80, and the minimum number of samples required was 102. The SPSS 21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY, USA) program was used for statistical analysis of the study data. The Shapiro-Wilk test was used to analyze the normal distribution of the data. The T-test was used to compare two groups with normally distributed data, while the Mann-Whitney U test was used to compare more than two groups with abnormally distributed data. The Wilcoxon signed-rank test was used to compare the dependent samples. In the analysis of repeated measures, percentage changes from baseline were calculated and compared using these values. The Pearson's chi-square, Fisher's Exact test, and the Fisher-Freeman-Halton Exact tests were used to analyze categorical data. The results were analyzed at the 95% confidence interval with a significance level of 0.05.

Results

Of the 150 patients who underwent laparoscopic cholecystectomy, 120 were enrolled in the study and 108 were found eligible to be included in the statistical evaluation (Figure 1).

No significant difference was detected between the groups regarding the demographic characteristics of the patients (Table 1).

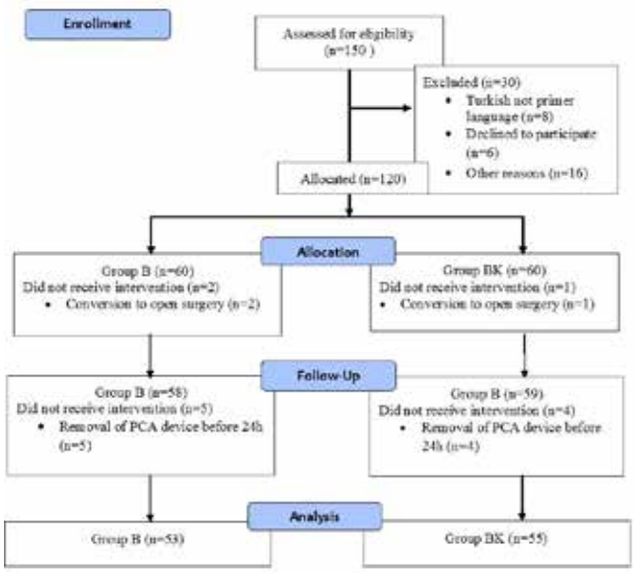

Figure 1. Trial flow diagram

Table 1. Demographic data of study groups

	Group B (n=53)	Group BK (n=55)	p
Age* (year)	46.88±13.78	48.09±13.38	0.646
Sex** (Male/Female)	9/44	16/39	0.124
BMI* (kg/m²)	27.45±2.72	27.52±3.59	0.904
ASA** (I/II)	24/29	25/30	0.442
Operation time* (minute)	45.18±12.55	41.90±13.55	0.195
Anesthseia time* (minute)	60.90±12.97	59.41±13.42	0.561

*Values are given as mean±standard deviation,
**Values are given as counts, BMI: Body mass index; ASA: American Society of Anesthesiologists;

When a comparison was made between the groups considering the HR and MAP levels, the HR level was observed to be significantly higher in Group BK after intubation ($p<0.05$) (Figure 2). However, there was no statistically significant difference between MAP and HR values of the groups measured at other times ($p >0.05$) (Figures 2, 3).

The VAS scores at 0, 2nd, 4th, and 24th hours and the DVAS scores at 0, 2nd, 4th, 12th and 24th hours were found to be significantly lower in Group BK than in Group B ($p<0.05$) (Figures 4, 5). The total amount of tramadol consumption recorded using a PCA device during the 24-h observation period was compared between the groups. The total consumption of tramadol was found to be lower in Group BK; however, there was no significant difference between the groups ($p>0.05$). Also, the time to first analgesic administration was significantly later in Group BK as compared to Group B ($p<0.0001$, Table 2).

No postoperative complications were observed in both groups. When evaluated in terms of subjects' satisfaction, we found that the patients in Group BK were significantly more satisfied than those in Group B ($p<0.05$).

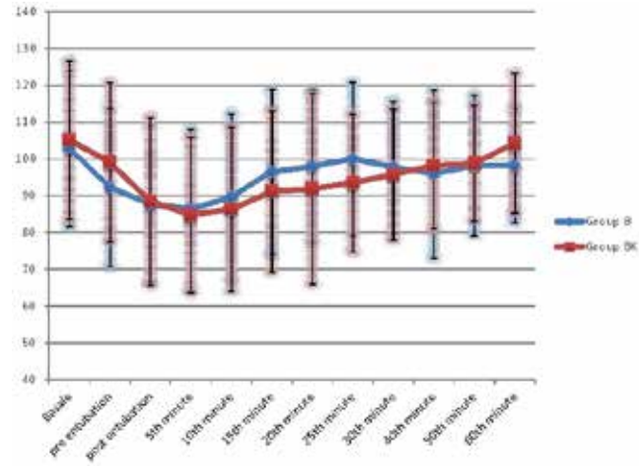

Figure 2. Mean values of Mean Arterial Pressure (MAP) according to groups

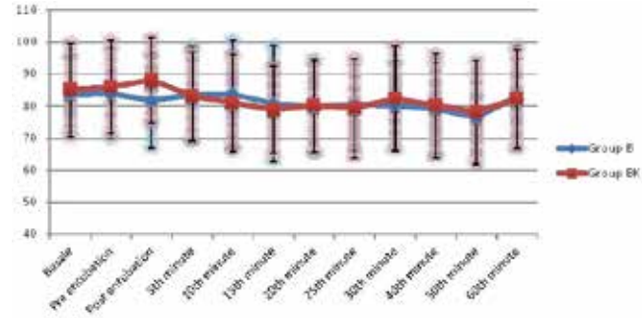

Figure 3. Mean values of Heart Rate (HR) according to groups

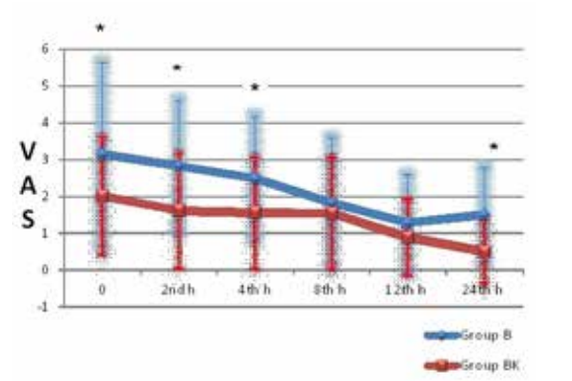

Figure 4. Mean values of Visual Analogue Scale (VAS) according to groups

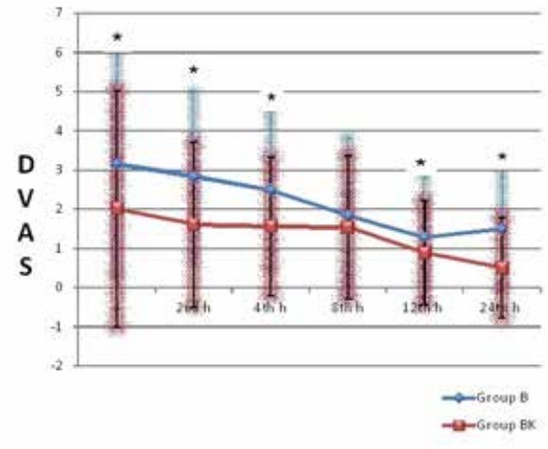

Figure 5. Mean values of Dynamic Visual Analogue Scale (DVAS) according to groups

Table 2. Analgesic usage profile of the groups

	Group B (n=53)	Group BK (n=55)	p
First analgesic time* (minute)	34.07±25.67	70.66±54.91	0.0001
Total tramadol consumption during 24h* (mg)	190.09±125.32	175.00±111.80	0.512
Requirement of rescue analgesics**	10 (18.9)	6 (10.9)	0.244

*Values are given as mean±standard deviation,
**Values are given as counts (%),

Discussion

We obtained lower VAS and DVAS scores in Group BK. No significant difference was detected between the groups in terms of total tramadol consumption in the first 24 hours of the postoperative period. The time to first analgesic administration was statistically longer in Group BK. Nevertheless, there was no statistically significant difference between the groups regarding the rescue analgesic administrations during the postoperative period.

Considering our literature review, it can be stated that researchers generally apply unilateral TAP block for adult patients using 15-30 ml local anesthetic agents in varying concentrations [10-13]. Bupivacaine, ropivacaine, and levobupivacaine are usually preferred local anesthetic agents for TAP block [1,14]. The administered concentration of bupivacaine varies between 0.125-0.5% [10,15]. In this study, we administered a 20 ml local anesthetic bilaterally. The concentration of bupivacaine was between 0.1425-0.25% in Group B and between 0.1125-0.25% in Group BK. We avoided local anesthetic systemic toxicity by administering low-dose bupivacaine in a fixed volume.

Several adjuvant agents (including epinephrine, clonidine, buprenorphine, tramadol, dexamethasone, dexmedetomidine, neostigmine) are added to local anesthetics in regional and peripheral block applications to provide effective, long and safe analgesia at one time [9]. Only a few studies have investigated the addition of local anesthetics for TAP block such as dexamethasone [11], epinephrine [12], fentanyl [15], and dexmedetomidine [16,17]. Previous studies have reported significantly lower postoperative morphine consumption in the dexmedetomidine group [16,17]. John et al. [15] did not show any statistically significant association between the total analgesic requirement and pain scores with the fentanyl group. We propose that our study may contribute to the literature by employing ketamine as an adjuvant agent for TAP block application.

Ketamine is an agent with anesthetic and analgesic properties and has attracted attention with its increasing use in recent years [18,19]. The efficacy of ketamine administration in regional anesthesia has been investigated in many studies [20-22]. In a study on the caudal block, ketamine 0.5 mg kg^{-1} added to bupivacaine 0.25% provided longer analgesia in comparison with the addition of clonidine 2 mcg kg^{-1} or epinephrine 5 mcg kg^{-1} to bupivacaine 0.25% [21]. In another study on caudal block application, it was suggested that as the ketamine intake increased (0.25, 0.5, and 1 mg kg^{-1}), the duration of analgesia prolonged after orchiopexy. However, a mild psychogenic side effect was recorded in the ketamine 1 mg kg^{-1} group in that study [22]. The ketamine dose administered in our study (0.5 mg kg^{-1}) was subanesthetic, but to the best of our knowledge, there is no evidence available in the literature indicating the lowest effective drug dose.

There are only a limited number of studies in the published literature regarding the use of ketamine in peripheral block applications. Use of ketamine has been reported in stellate ganglion blockage [23] and peritonsillar infiltration [24]. In both studies, effective analgesia was achieved in the ketamine-receiving groups without any significant postoperative side effect [23,24]. In a study comparing three groups of patients receiving IV ketamine 0.5 mg kg^{-1}, subcutaneous (SC) ketamine 0.5 mg kg^{1}, and placebo at the end of the tonsillectomy procedure, pain score and analgesic consumption were found to be significantly lower in the ketamine groups, but the efficacy of both ketamine groups was similar [25].

No hemodynamic difference was found in the peritonsillar infiltration study performed with ketamine [24] and the TAP block study with dexmedetomidine [17]. In this study, we applied hemodynamic monitoring to all patients and did not find any difference between the groups except that the MAP levels were significantly higher in Group BK.

When the groups were compared in terms of VAS and DVAS scores, the VAS scores at 0, 2^{nd}, 4^{th}, and 24^{th} hours and the DVAS scores at 0, 2^{nd}, 4^{th}, 12^{th} and 24^{th} hours were found to be significantly lower in Group BK as compared to Group B. The time to first analgesic requirement was significantly longer in Group BK (70.66 min) than in Group B (34.07 min). No significant difference was observed between the groups regarding tramadol consumption during the first 24h which may be due to the preventive analgesia in both groups and the mean VAS scores of both groups were below 4.

There are some limitations of this study. Firstly, we didn't use a control group. The lack of a fixed concentration of bupivacaine and not monitoring the depth of anesthesia can be listed as the other limitations of this study. Also, the serum concentrations of the drugs administered in the TAP block were not estimated. Additionally, the fact that the doses of adjuvant ketamine were not specified in previous studies can be considered as a limitation.

In our study, we applied multimodal analgesia by using TAP block, IV PCA with tramadol and IM nonsteroidal anti-inflammatory drugs for laparoscopic cholecystectomy. We can conclude that using a combination of bupivacaine plus ketamine rather than bupivacaine alone for TAP block can reduce pain scores; prolong the time to first analgesic requirement and enhance patients' satisfaction. However, ketamine does not seem to affect tramadol consumption. Consequently, we believe that ultrasound-guided TAP block with bupivacaine and ketamine combination can be an alternative to other analgesic methods for postoperative pain management after laparoscopic cholecystectomy.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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